IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Allison Hubel	Examiner: Elli Peselev
Serial No.:	09/458,862	Group Art Unit: 1623
Filed:	December 10, 1999	Docket: 600.451US1
Title:	COMPOSITIONS AND METHODS FOR CRYOPRESERVATION OF PERIPHERAL BLOOD LYMPHOCYTES	

APPELLANT'S REPLY TO EXAMINER'S ANSWER

Mail Stop Appeals
Commissioner for Patents
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Sir:

This Reply is presented in response to the Examiner's Answer, mailed December 10, 2003, to Appellant's Brief on Appeal, filed on September 24, 2003. Appellant's Brief on Appeal was filed in response to the rejection of claims 1-8, 11-12, 14, 16-17, 19-22, 24, 26-28, 30-34, 37-44, and 47-58 of the above-identified application.

Appellant's Reply is filed in triplicate. Please charge any required additional fees or credit overpayment to Deposit Account 19-0743.

REPLY

The Examiner made several statements in the Examiner's Answer that Appellant will now reply to.

I. Enablement Rejection Under 35 U.S.C. § 112(1)

A. The Examiner's Answer

In the Examiner's Answer, the Examiner asserts that Appellant has failed to provide any teaching or guidance on how to obtain compounds which are structurally distinct from arabinogalactan but which are biological or functional equivalents thereof, and that it would take an undue amount of experimentation by a person having ordinary skill in the art at the time the instant invention was made to determine which specific compounds are biological or functional equivalents of arabinogalactan.

B. Rebuttal to Examiner's Answer

As discussed in the Appeal Brief, Appellant's specification discloses that arabinogalactan, or a biological or a functional equivalent thereof, includes an agent that is useful as a hematopoietic cell cryoprotective agent and lacks the cytotoxicity of DMSO, and includes naturally occurring or synthetic arabinogalactan, portions of arabinogalactan, such as degradation products, and chemically or biochemically modified arabinogalactan or portions thereof which have been modified (page 4, lines 6-16). Arabinogalactan is a natural polysaccharide, and sources of arabinogalactan are commercially available as described in PCT/US97/04764 (WO 97/35472) and U.S. Patent No. 5,116,969 (both of record). Chemically or biochemically modified arabinogalactans are disclosed in U.S. Patent Nos. 5,478,576 (of record) and 5,116,969, which were incorporated by reference into the specification.

Moreover, the claims recite that the amount of arabinogalactan, or a biological or a functional equivalent thereof, in the cryopreservation medium has certain specific properties. For instance, the arabinogalactan, or a biological or a functional equivalent thereof, is present in an amount which results in a high post-thaw survival rate for cryopreserved lymphocytes, hematopoietic stem cells, or lymphocytes which are activated or genetically modified *ex vivo*. The specification discloses that a "high survival rate" means that at least about 40%, preferably at least about 50%, more preferably at least about 60%, and even more preferably at least about 80%, of cryopreserved cells are viable upon thawing (page 4, lines 16-19). Methods to determine the viability and recovery of cells after freezing and thawing are discussed at pages 24-25 and in Examples 1 and 2 of the specification. Exemplary cryopreservation media are described at pages 14-16 and in Example 1 of the specification. Thus, one skilled in the art in possession of Appellant's specification is provided guidance on how to obtain a biological or functional equivalent of arabinogalactan and determine if that biological or functional equivalent of arabinogalactan has the recited property.

The factors to be considered in determining whether it would require undue experimentation by one skilled in the art in possession of an Appellant's specification to identify biological or functional equivalents of arabinogalactan include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1985).

As mentioned above, the specification provides a significant amount of direction and guidance in modifications to arabinogalactan and actual working examples of compositions and methods which employ arabinogalactan and are useful to cryopreserve cells such as lymphocytes (factors 2 and 3).

The skill of those in the art (factor 6) is high in the fields of molecular biology and immunology, as acknowledged by the court in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) and *Enzo Biochem. Inc. v. Calgene Inc.*, 188 F.3d 1362, 52 U.S.P.Q. 1129 (C.A.F.C. 1999). And the use of DMSO, and glycerol with serum, in cryopreservation compositions with peripheral blood lymphocytes, was known (factor 5) (see specification at page 2, line 6 to page 3, line 11). Of course, compositions comprising arabinogalactan, or a biological or a functional equivalent thereof, useful to cryopreserve freshly isolated lymphocytes, hematopoietic stem cells or lymphocytes which are activated or genetically altered *ex vivo* was not in the art.

With respect to quantity of experimentation, and the predictability of the art (factors 1 and 7), the fact that the outcome of a synthesis/screening program is unpredictable is precisely why a screening program is carried out. The Board simply cannot reasonably contend that a screening program to locate biomolecules with target biological properties would not be carried out by the art worker because the results cannot be fully predicted in advance. Moreover, the Federal Circuit has explicitly recognized that a need to carry out extensive synthesis and screening programs to locate bioactive molecules does not constitute undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988). In *Wands* the court held that a process of immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics did not require undue experimentation. The Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners having skill in the art related to the present application would be well-equipped to screen molecules to locate those with the recited properties.

Considering the *Wands* factors, it clearly would not require undue experimentation to identify molecules commensurate in scope with the pending claims. Accordingly, Appellant's specification fully enables the claimed invention.

II. Rejection under 35 U.S.C. § 103(a) over WO 97/35472

A. The Examiner's Answer

In the Answer, the Examiner states that although lymphocytes are not specifically disclosed by WO 97/35472, the term "somatic cells" at page 9, lines 25-31 and page 10, lines 1-10, encompasses lymphocytes and that a person having ordinary skill in the art at the time the instant invention was made would have been motivated to use the cryopreservation medium disclosed by WO 97/35472 for any somatic cells, including lymphocytes especially since WO 97/35472 discloses that two of the most widely used cryopreservative agents, DMSO and glycerol, are damaging to thawed cells (page 2, lines 30-31 and page 3, lines 1-2) but that the presence of arabinogalactan in the media reduces cellular damage (page 8, lines 5-11).

B. Rebuttal to Examiner's Answer

As discussed below and in the Appeal Brief, none of the three elements required to establish a *prima facie* case of obviousness have been put forth by the Examiner.

Appellant's invention is directed to cryopreservation compositions containing arabinogalactan, or a biological or a functional equivalent thereof, and methods which employ those compositions, for cells that are used in cell therapy, cells which are known to have lower viabilities in standard media (see paragraph 3 of the Bischof Declaration, of record), which compositions and methods provide for high post-thaw viability of those cells.

WO 97/35472 discloses that there was no difference in post-thaw viability for 4/5 of the arabinogalactan-containing test media relative to "the industry standard" (cell culture medium + serum + DMSO) (page 14, lines 10-13), while cells frozen in media with arabinogalactan and serum had reduced viability (page 14, lines 13-15). WO 97/35472 also discloses that there was "substantially no difference" in plating efficiency at day 1 for 6/7 of the cell types tested, and that at day 6 post-thaw, there was "substantially no difference" between treatment groups (page 14,

lines 23-24, and page 14, line 29-page 15, line 2). Table 2 in WO 97/35472 shows the ranking of the six tested media with respect to growth rates (day 6/day 1) for one cell line, CPAE cells. WO 97/35472 then concludes that arabinogalactan "can be used to replace serum in a standard freezing medium, in a formulation with DMSO, for all cell types studied" and that freezing in 50% w/v arabinogalactan was better or equivalent to the standard media for 5/7 cell types tested (emphasis added; page 15, lines 20-31).

Thus, although a medium which lacks DMSO and serum and has a very high percent of arabinogalactan (50%) was at least equivalent to standard freezing media for 5/7 of the cell types tested in WO 97/35471, a lower percent of arabinogalactan (< 50%) was not able to successfully replace DMSO in a standard freezing medium. Further, given that there was no difference in post-thaw viability for 4/5 of the tested media relative to "the industry standard," the use of arabinogalactan-containing cryopreservation media, e.g., media with < 50% arabinogalactan, to cryopreserve any cell type has no apparent advantage over "the industry standard".

Accordingly, WO 97/35472 fails to provide the requisite motivation to arrive at Appellant's invention as WO 97/35472 teaches away from the use of cryopreservation media lacking DMSO and containing < 50% arabinogalactan to cryopreserve cells, and particularly cells useful in cell therapy, i.e., those with lower viabilities in standard media.

With respect to establishing the reasonable expectation of success needed to support a *prima facie* case of obviousness, the Examiner has provided no evidence that the general disclosure in WO 97/35472 would provide one of ordinary skill in the art with a reasonable belief that freshly isolated lymphocytes, hematopoietic stem cells, or lymphocytes which are activated or genetically modified *ex vivo* and cryopreserved with arabinogalactan, or a biological or functional equivalent thereof, in the absence of DMSO would have high survival rates post-thaw.

In contrast, Appellant has provided extensive evidence that one of ordinary skill in the art at the time of Appellant's filing would not reasonably expect that a particular cryopreservation media useful for one cell type would be useful for another cell type (see Sputtek et al., the Hubel article, and the Declarations of Dr. Hubel and Dr. Bischof, all of record). For instance, as discussed in the Appeal Brief, certain cell types, such as granulocytes (a "blood" cell), cannot be cryopreserved at all (paragraph 5 of the Hubel Declaration), and conditions employed to freeze

red blood cells are suboptimal for the preservation of viable white blood cells (Sputtek et al., In: Clinical applications in Cryobiology, CRC Press (1991), of record). In addition, in her Rule 132 Declaration, Dr. Hubel discussed the factors which influence cell viability after cryopreservation and provided evidence supporting the differences in survival rates for different cryopreserved cell types. In view of those differences and WO 97/35472, Dr. Hubel concluded that a general disclosure of a method of freezing cells which employs an arabinogalactan-containing freezing medium useful for one cell type, such as that in WO 97/35472, does not enable a method or composition useful for another cell type due to differences in the biophysical and biological properties of each particular type of cell (paragraph 11 of the Hubel Declaration).

After discussing the state of the art prior to Appellant's filing, such as the factors known to influence the utility of cryopreservation media, and considering the disclosure in WO 97/35472, Dr. Bischof in his Rule 132 Declaration concluded that WO 97/35472 did not provide a reasonable expectation that the protocols and solutions disclosed therein would be useful for other cell types and, in particular, for cells such as freshly isolated lymphocytes, hematopoietic stem cells, or *ex vivo* modified lymphocytes (paragraphs 4 and 6 of the Bischof Declaration). Dr. Bischof also concluded that WO 97/35472 did not provide a reasonable expectation that the use of any particular arabinogalactan-containing solution would result in a threshold level of post-thaw viability for cells employed in cellular-based therapies (paragraph 6 of the Bischof Declaration).

Further, the Examiner's Answer has failed to articulate the reasons why the Rule 132 Declarations, Sputtek et al., and the Hubel article taken together are insufficient to overcome the alleged *prima facie* case of obviousness. M.P.E.P. 716.01(d) and M.P.E.P. 2144.08(III).

Finally, the present claims recite elements which are not disclosed in WO 97/35472. For instance, WO 97/35472 indicates that the described media may be employed with a variety of cell types including human cells (page 5, line 2), and "somatic," "blood" or "immune" cells (page 9, lines 25-31, page 10, line 4, and page 11, line 30), as well as genetically altered cells (page 10, line 9). Nevertheless, blood is known to include a variety of cell types such as erythrocytes, lymphocytes, monocytes, neutrophils, eosinophils, and basophils (pages 233 and 1030 of Churchill's Medical Dictionary, Churchill Livingstone, Inc. (1989), of record), "immune cells"

include T cells, B cells, plasma cells and macrophage (page 920 in Churchill's Medical Dictionary, Churchill Livingstone, Inc. (1989), of record).

Specifically, WO 97/35472 does not disclose or suggest cryopreservation media comprising freshly isolated lymphocytes, hematopoietic stem cells or lymphocytes which are activated or genetically modified *ex vivo* (Groups I-VI); an amount of arabinogalactan, or a biological or functional equivalent thereof, that results in a high post-thaw survival rate for freshly isolated lymphocytes, hematopoietic stem cells or lymphocytes which are activated or genetically modified *ex vivo* (Groups I-III); a cryopreservation medium with lactated Ringer's solution, PlasmaLyte-A™, Normosol-R™, Veen-D™, Polysal®, or Hank's balanced salt solution (Group III); a cryopreservation medium comprising freshly isolated lymphocytes, hematopoietic stem cells or lymphocytes which are activated or genetically altered *ex vivo*, and 0.5% to about 20% glycerol and 1% to 40% arabinogalactan, which are present in an amount that results in high post-thaw survival rate for those cells (Groups IV and V); or a cryopreservation composition comprising arabinogalactan, or a biologicial or functional equivalent thereof, and freshly isolated lymphocytes, hematopoietic stem cells or lymphocytes which are activated or genetically modified *ex vivo*, which composition results in an about 40% post-thaw survival rate for those cells (Group VI).

The Board is also respectfully requested to consider that WO 97/35472 discloses that glycerol is "damaging." Hence, WO 97/35472 teaches away from glycerol containing cryopreservation media (Groups IV and V).

Further, even if one of ordinary skill in the art had believed it was possible that arabinogalactan, or a biological or functional equivalent thereof, could cryopreserve freshly isolated lymphocytes, hematopoietic stem cells or lymphocytes which are activated or genetically altered *ex vivo*, there would be no reason to expect that cryopreservation of freshly isolated lymphocytes, hematopoietic stem cells or lymphocytes which are activated or genetically altered *ex vivo* in a medium containing certain amounts of arabinogalactan, or a biological or functional equivalent thereof, results in about 40% post-thaw survival rate for those cells (claims 59-60; Group VI).

Therefore, Appellant's invention is not *prima facie* obvious.

CONCLUSION

Each of the pending claims subject to this appeal is patentable and, in particular, meets the requirements of 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103(a). Appellant believes the claims are in condition for allowance and requests withdrawal of the § 112(1) and § 103(a) rejections of claims 1-8, 11-12, 14, 16-17, 19-22, 24, 26-28, 30-34, 37-44, and 47-58.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop Appeals, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 9th day of February, 2004.

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